PATENT
Attorney Docket No. 12636-219

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Jorge DiMartino	Group Art Unit: 1623
Application No.: 09/976,468	Confirmation No.: 9964
Filed: October 12, 2001	Examiner: LEWIS, Patrick
For: Composition And Method For Treating Graft-Versus-Host Disease	Client No. 021971

DECLARATION UNDER 37 C.F.R. §1.132

I, Joi S. Ninomoto, declare as follows:

1. I am currently Vice President of Medical Affairs at SuperGen, Inc., Dublin, California. I am in charge of the Clinical Direction, management and execution of Phase IV Clinical Trials, the Medical Science Liaison Program, the Medical Communications Program as well and the Publication Planning Program. The detail of my education and professional experiences is provided in the attached *curriculum vitae* of mine.

2. Under the sponsorship and general direction of Jorge DiMartino, M.D., Ph.D. of SuperGen, Marco de Lima, M.D. conducted a phase I/II clinical trial of pentostatin for graft-versus-host disease (GVHD) prophylaxis at Department of Blood and Marrow Transplantation, M.D. Anderson Cancer Center, Houston.

3. The results of the phase I/II clinical trial of pentostatin for GVHD prophylaxis were reported to me in an interim analysis of the trial. I hereby summarize the design, procedures and results of this clinical trial below.

4. This trial is an adaptive, randomized, dose-finding study that takes into account toxicity and efficacy in a Baysean "play the winner" design. The "winner" dose moves to the phase II portion of the study. Probability of assignment to the control group was fixed at 20%. Recipients of unrelated donor (UD) and matched related donor (MRD) stem cell transplants are eligible. Success was defined as being alive, engrafted, in complete remission (CR), without GVHD at study completion (100 days post hematopoietic stem cell transplantation (HSCT)). Development of grade III-IV acute GVHD (aGVHD) defined failure at any time, while grade I-II did not constitute failure if absent by day 100. This design has power 0.7 to detect a dose that has a success rate of 60% for low-risk patients (human leukocyte antigen (HLA) matched, in CR) and 45% for high-risk patients (mismatched, not in CR). High-resolution typing was available for all donor-recipient pairs at HLA-DB1 and –DQB1 loci, and to 83% of the pairs at HLA-A and –B loci; all patients had low-resolution –C typing.

5. All patients received tacrolimus (tacro) from day -2 (target level of 5-15 ng/ml) and methotrexate (MTX) at 5 mg/m^2 on days +1, +3, +6. On day +11 only the control group received MTX. Pentostatin was given on days +8, +15, +22 and +30, in treatment arms at 0.5 mg/m^2, 1 mg/m^2, 1.5 mg/m^2, and 2 mg/m^2.

6. Seventy-three (73) patients (median age 45 yrs; range 18-72) have been enrolled. Diagnosis were acute myeloid leukemia (AML) / myelodysplastic syndromes (MDS) in 48 patients; acute lymphoblastic leukemia (ALL) in 8 patients; chronic myelogenous leukemia (CML) in 10 patients; non-Hodgkin's Lymphoma (NHL) in 7 patients; and 58% of the patients were not in CR at HSCT. Conditioning regimens were bulsulfan based (n=52), melphalan based (n=10), BEAM (n=2), and CyTBI (n=9); 71% were ablative and 29%, reduced intensity. ATG was used in the regimen in 86% of the cases. Stem cell source was from bone marrow (n=67) and peripheral blood (n=6). Donors are UD (n=67) and MRD (n=6). Proportion of patients with

donor-recipient HLA mismatches was 24%, 20%, 33%, 21% and 40%, respectively for the 5 study arms; median age was similar. Eighty-five percent (85%) of the intended pentostatin doses were delivered.

7. In the trial it was found that pentostatin did not delay engraftment. Incidents of toxicities (control vs. study arms): renal (all grade I/II) = 47% vs. 36%; TTP/HUS = 12% vs. 9% (more severe among pentostatin patients); early relapse =12% vs. 5%; engraftment failure = 6% vs. 3%; and delayed engraftment (>21 days) = 0% vs. 5%. The results of pentostatin for GVHD prophylaxis are summarized in the table below.

Pentostatin dose	control group (n=17)	0.5 mg/m² (n=10)	1 mg/m² (n=12)	1.5 mg/m² (n=24)	2 mg/m² (n=10)
gd II-IV aGVHD	47%	44%	63%	29%	50%
gd III-IV aGVHD	20%	33%	27%	10%	10%
CMV reactivation	41%	30%	33%	50%	50%
bact/fungal infection	59% / 12%	60% / 10%	50% / 18%	55% / 17%	70% / 10%
Not evaluable	n=2	n=1	n=1	n=4	n=0
Failure rate	47%	70%	33%	29%	40%

8. The results of this phase I/II clinical trial demonstrate that pentostatin is efficacious in preventing and/or reducing GVHD in transplant recipients without interference with engraftment. As shown in the table above, patients receiving pentostatin at the dose of 1.5 mg/m² had the lowest number of incidents of developing grade II-IV aGVHD (failure rate of 29%). In contrast, the control group without treatment with pentostatin has a failure rate of 47%. Also significantly, only 10% of the patients in the treatment arms of pentostatin at 1.5-2 mg/m² developed grade III-IV aGVHD, compared with 20% in the control group.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: _____

Joi S. Ninomoto, Pharm.D.

Date: 7/25/05 Country of Citizenship: USA

Address

Residence: 3218 Colebrook Lane, Dublin CA 94568

CURRICULUM VITAE

Joi Suzuki Ninomoto, PharmD

3218 Colebrook Lane
Dublin, CA 94568
(925) 361-7070

SuperGen, Inc
Medical Affairs
4140 Dublin Blvd, Suite 200
Dublin, CA 94568
(800) 353-1075 x 198

Pharmacy Licensure:
California #45915
Massachusetts #21551

QUALIFICATIONS

Experience in strategic analysis, project planning, medical writing, clinical research, and review of scientific and clinical literature. Working knowledge of regulatory guidelines for the management and support of the Medical Affairs, Clinical, Marketing, and Sales departments. Excellent communication, presentation, teambuilding and organizational skills.

PROFESSIONAL EXPERIENCE

SuperGen, Inc, Dublin, CA

Vice President, Medical Affairs	Feb. 2005 – present
Executive Director, Medical Affairs	April 2004 – Feb. 2005
Director, Medical Affairs	June 2001 – April 2004
Associate Director, Medical Affairs	July 1999 – June 2001
Manager, Professional Services	Aug. 1998 – July 1999

Assume the leadership role in the Medical Affairs organization with overall responsibilities in the following areas: Medical Communications, Investigator-sponsored studies/Phase IV Clinical Trials Program, Professional Services (Medical Science Liaisons) and Strategic Publication Planning. Provide strategic and operational direction, as well as oversight for these programs. Report directly to the Chief Operating Officer. Develop organizational infrastructure to support the post-marketing programs for Nipent® and in-licensed late stage products. Ensure that the Medical Affairs programs are fully integrated with the overall corporate commercialization plan. Plan and direct post-marketing clinical strategies for the continued corporate growth and development of SuperGen's approved and late stage products. Provide clinical and technical support to Sales, Marketing, Clinical Research, Regulatory Affairs, Quality Assurance, Commercial Operations and Project Management.

Major accomplishments include creation of departmental mission statement, core values, and core competencies documents; creation of departmental goal tracking for key projects; successful conversion of Medical Communication's inquiry/response to a paperless system; creation of an electronic library; restructuring of the Phase IV program from a broad to a clinically focused program with integration of metrics and ROI evaluations; and creation of a Strategic Publication Planning team.

Specific Responsibilities and Oversight:

- Phase IV Clinical Trial Program:
  Oversee Phase IV Clinical Trial team that manages the planning, execution and budgets for Phase IV and investigator-initiated studies that focus on the clinical advancement of SuperGen's marketed and late stage products. Provide strategic and operational direction and insure that all project-related objectives and timelines for Phase IV clinical trials are met and are in accordance with FDA and ICH guidelines, and SuperGen's SOPs. Assist with the development of protocol designs. Work closely with MSLs and key opinion leaders in the clinical development of SuperGen's approved and late stage products.

- Medical Science Liasons Program:
  Oversee the MSL team that establishes productive relationships with high-level professional advocates by disseminating SuperGen's cutting edge medical and clinical information KOLs, and by capiltaizing on new clinical and business opportunities through dissemination of novel data from KOLs back to key internal colleagues. Provide strategic and operational direction and insure that all project-related objectives and timelines for MSL programs are met and are in accordance with OIG and AMA Guidelines and the Pharma Code.

- Strategic Publication Planning:
  Oversee Strategic Publication Planning Team for approved and late stage products. Lead SuperGen core team (Medical Affairs, Marketing, & Clinical) in developing publication strategy and tactics, and work with outside vendors to analyze and position products in the marketplace (analyses include literature audits, message mapping, gap analysis, and competitive analysis). Work with vendors to create timely publications from clinical and Phase IV programs that support SuperGen's key messages and facilitate in product adoption.

- Drug Information / Medical Communications:
  Train and direct the Medical Affairs team that provides clinical and technical information on SuperGen products and related therapeutic areas to health care professionals and patients. Responsibilities include responding to medical questions by using clinical judgment, interpreting and analyzing medical literature, conveying information to specialized medical personnel and laymen, as well as overseeing and training SuperGen personnel to perform the above functions. Responsibilities also include making decisions on operations of department, and overseeing personnel in charge of the customer inquiry management database as well as the medical literature database. Also responsible for maintaining medical and technical expertise by attending professional meetings.

- Education – Sales, Marketing, and Clinical Research:
  Oversee Medical Affairs team that analyzes, creates, and edits educational materials and clinical publications for internal and external customers. Examples include editing Marketing promotional pieces and educational slide kits for clinical accuracy and product positioning, creating educational pieces and sales training material, editing SuperGen sponsored clinical abstracts for meeting proceedings such as ASH and ASCO, assisting investigators with creation of clinical presentations for meetings, creating and updating study reports and clinical drug Investigator

Brochures, reviewing and editing study protocols submitted to SuperGen for medical soundness and business strategy, and editing Investigator's manuscripts intended for publication submission. Key skills include finding and analyzing medical literature (pertaining to SuperGen products, the competition, and diseases under investigation), extracting key data using clinical judgment that will help position SuperGen products in the marketplace, and creating credible SuperGen friendly messages using medical writing skills. Responsibilities also include training SuperGen personnel to perform the above functions, development of Core Curriculum training program for in-house CRAs, and overseeing Journal Club. Key customers include the SuperGen's Clinical Research, Sales, and Marketing Departments.

- Regulatory:
  Train and oversee Medical Affairs team that provides clinical and technical support to SuperGen's Regulatory Department. Responsibilities include creating or assisting with creation of sections of sNDA and NDA submissions, orphan drug submissions to the FDA, Annual Safety Reports for the FDA, and package inserts and other labels. Skills required include full understanding of various oncologic diseases and their treatment, working knowledge of regulatory guidelines as well as good medical writing skills. Responsibilities also include serving as acting Medial Safety Monitor for Nipent® SAEs (serious adverse events) reported in SuperGen clinical studies by interpreting clinical data received from trials, determining if additional clinical information is needed from investigators, communicating with investigational sites, and interacting with Medical Safety and Regulatory Departments in filing reports to the FDA. Responsibilities also include training Medical Affairs personnel as Safety Monitors per above.

- Clinical:
  Assist in NDA planning and various projects as needed (CSRs and NDA submissions).

- Quality Assurance:
  Responsible for providing clinical and technical support to Quality Assurance, including creating SOPs, assessing medical and business issues surrounding product liability and determining possible resolution to product issues by participating on the Material Review Board. Also oversee Customer Compliant Representative that handles tracking of issues and communication to customers leading to resolution of issues.

- Business Development:
  Responsible for clinically analyzing potential products for possible in-licensing opportunities. Specific responsibilities include analyzing potential products for clinical compellingness, clinical development programs, publication strategies and plans, and competitive marketplace and fit with SuperGen corporate direction. Actively participate in due diligence meetings.

- Commercial Operations:
  Responsible for providing clinical and technical support to Commercial Operations, including creating reports related to drug positioning in various disease states.

- Project Management:
  Assist with project planning, assist team leaders with various projects by lending clinical and drug development knowledge, and lead multi-disciplinary teams on various task forces. Examples include Orathecin packaging, stability, specialty distribution, and Expanded Access projects.

Amgen Corp, Thousand Oaks, CA
Associate Manager, Professional Services — Aug. 1996 – Aug. 1998
Senior Professional Services Specialist — Aug. 1995 – Aug. 1996

- Provided clinical and technical information on Neupogen® and related therapeutic areas to health care professionals and patients.

- Provided clinical and educational support for the Sales and Marketing Division, including development of educational tools and programs, sales training, customer education, opinion leader development, competitive intelligence, and managing clinical projects. Served as preceptor for clinical pharmacy clerkship students.

- Provided support to Product Development Teams on clinical projects and served as liaison between the Professional Services Department and Product Development Teams in the Clinical Development Division.

Dana Farber Cancer Institute, Boston, MA
Clinical Pharmacist — Aug. 1994 – Aug. 1995

- Created Clinical Pharmacy position and acted as a consultant to physicians and nurses on daily patient medical rounds, trained pharmacy staff, precepted PharmD and undergraduate pharmacy students.

The University of Texas M.D. Anderson Cancer Center, Houston, TX
Clinical Pharmacy Oncology Resident — July 1993 – July 1994

- Completed residency training with emphasis in hematology and stem cell transplant, completed residency research project with publication. Assisted oncology physicians with patient accrual into study protocols, edited protocols for clinical accuracy, wrote and amended daily chemotherapy and supportive care medication orders based on clinical judgment.

New England Deaconess Hospital, Boston, MA
Per Diem Staff Pharmacist — Aug. 1991 – April 1993

- Entered medication orders, admixed and dispensed medications using good clinical judgment. Supervised pharmacy students and technicians. Performed Drug Utilization Evaluations.

University of California at San Francisco, Department of Hematology/Medicine
Research Associate — Feb. 1987 – Aug. 1988

- Analyzed RFLPs in the human alpha-globin gene cluster of sickle cell anemia patients using radio-labeled nick translations and southern blots.

EDUCATION AND TRAINING

ASHP accredited Residency in Oncology Pharmacy Practice
The University of Texas M.D. Anderson Cancer Center, Houston, TX
July 1993 – July 1994

Doctor of Pharmacy
Massachusetts College of Pharmacy and Allied Health Sciences, Boston, MA
Sept. 1991 – June 1993

Bachelor of Science in Pharmacy
Massachusetts College of Pharmacy and Allied Health Sciences, Boston, MA
Sept. 1998 – Dec. 1990

Bachelor of Sciences in Genetics
University of California at Davis
Sept.1981 – June 1986

FACULTY APPOINTMENT

Adjunctive Assistant Professor of Clinical Pharmacy
Massachusetts College of Pharmacy and Allied Health Sciences
Jan. 1995 – Aug. 1995

TEACHING

Preceptor for Massachusetts College of Pharmacy and Allied Health Sciences, and Northeastern University Bouve College of Pharmacy Undergraduate Pharmacy Students' Clinical Clerkship, and PharmD Students' Oncology Rotation (clinical site: Dana Farber Cancer Institute)
Aug. 1994 – Aug. 1995

Guest Lecturer for Northeastern University Bouve College of Pharmacy PharmD Students – lecture on Principles and Complications of Bone Marrow Transplantation, April 1995

Preceptor for University of Texas PharmD Student's Oncology Rotation, lectures on Principles of Bone Marrow Transplantation, and Principles of Nutritional Support
Feb 1994

Guest Lecturer for University of Texas Medical Students – lecture on Principles of Nutritional Support
Nov 1993

Guest Lecturer for University of Houston Undergraduate College of Pharmacy Therapeutics Course, Oncology Block – lecture on Mucositis
Sept. 1993

Preceptor for Massachusetts College of Pharmacy Undergraduate Pharmacy Student's Clinical Clerkship (clinical site: Beth Israel Hospital)
Jan. 1993 – Mar. 1993

Preceptor for Massachusetts College of Pharmacy Undergraduate Professional Pharmacy Practice Laboratory
Sept. 1991 – May 1992

Guest Lecturer for Massachusetts College of Pharmacy Undergraduate Pharmacy Course, Introduction to Prescription Medications – lecture on Analgesic and Anti-inflammatory Agents
Feb. 1992

RESEARCH

Residency:

Pharmacokinetics of FK-506 Metabolites in Allogeneic Bone Marrow Transplant Recipients.
Preceptors: Cindy Ippoliti, PharmD and Donna Przepiorka, MD, PhD
1993-1994

Other:

Extended Stability of Taxol in Glass Containers.
Preceptors: Steve Steckel, PharmD and David Williams PhD
(funded in part by Bristol Myers-Squibb)
1993

RFLPs in the Human Alpha-globin Gene Cluster in Sickle Cell Anemia Patients.
Preceptor: Stephen Embury, MD
(sponsored by NIH)
1987-1988

Endogenous Retroviral Sequences in Human Colon Cancer Cell Lines.
Preceptor: Hardy Chan, PhD
(sponsored by NIH)
Presented at the Syntex Corp, Research Conference, 1984

PUBLICATIONS

Blood Tacrolimus concentration unchanged by plasmapheresis.
Prezepiorka D, Suzuki J, Ippoliti C, Hester JP, Fritsche HA.
AJHP 1994; 15(7): 1708

Two Bgl II RFLPs of the human alpha-globin gene cluster in the American sickle cell population.
Embury S, Blachman T, Kropp G, Suzuki J, Boyle M.
Nucleic Acids Res. 1989 Nov 11;17(21):8903.

PLATFORM PRESENTATIONS

A Pharmacokinetic Study of FK-506 Metabolites in Bone Marrow Transplant Recipients.
Alcalde VIII Southwest Leadership Conference, San Antonio, TX,1994
and ASHP Southwestern States Resident's Conference, Little Rock, AR, 1994

HONORS AND AWARDS

Rho Chi Pharmacy Honor Society
Syntex Corp, Co-operative Study, Recombinant DNA lab, Palo Alto, CA

ORGANIZATIONS

American Medical Writers Association
    Certificate in Multidisciplinary Medical Writing: in progress
Drug Information Association
    Certificate in Medical Communications
American Society of Health-System Pharmacists

REFERENCES

Available upon request